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Anders Helander, Olof Beck, Robert Hägerkvist & Peter Hultén

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ORIGINAL ARTICLE

Identification of novel psychoactive drug use in Sweden based on laboratory analysis – initial experiences from the STRIDA project

ANDERS HELANDER¹, OLOF BECK², ROBERT HÄGERKVIST³ & PETER HULTÉN³

Departments of ¹Laboratory Medicine and ²Medicine, Karolinska Institutet and Karolinska University Laboratory, and ³The Swedish Poisons Information Centre, Stockholm, Sweden

Abstract

Aim. The study aimed to collect information concerning the increasing use of new psychoactive substances, commonly sold through online shops as ‘Internet drugs’ or ‘legal highs’, or in terms of masked products such as ‘bath salts’ and ‘plant food’. **Methods.** The Karolinska Institutet and Karolinska University Laboratory and the Swedish Poisons Information Centre have initiated a project called ‘STRIDA’ aiming to monitor the occurrence and trends of new psychoactive substances in Sweden, and collect information about their clinical symptoms, toxicity and associated health risks. A liquid chromatographic-tandem mass spectrometric (LC-MS/MS) multi-component method has been developed, currently allowing for the determination of > 80 novel psychoactive compounds or metabolites thereof. This study focused mainly on the particular drug substances identified and the population demographics of the initial STRIDA cases. **Results.** In urine and/or blood samples obtained from 103 consecutive cases of admitted or suspected recreational drug intoxications in mostly young subjects (78% were ≤ 25 years, and 81% were males) presenting at emergency departments all over the country, psychoactive substances were detected in 82%. The substances comprised synthetic cannabinoids (‘Spice’; JWH analogues), substituted cathinones (‘bath salts’; e.g. butylone, MDPV and methylone) and tryptamines (4-HO-MET), plant-based substances (mitragynine and psilocin), as well as conventional drugs-of-abuse. In 44% of the cases, more than one new psychoactive substance, or a mixture of new and/or conventional drugs were detected. **Conclusion.** The initial results of the STRIDA project have documented use of a broad variety of new psychoactive substances among mainly young people all over Sweden.

Key Words: Cannabinoids, cathinone, designer drugs, indoles, Internet, mass spectrometry/methods, substance abuse detection, tryptamines

Introduction

In recent years, an increasing number of synthetic and plant-based psychoactive substances and products have appeared on the recreational drug market [1]. The new drugs include a wide range of synthetic cannabinoids, phenylethylamines and tryptamines that are intended to mimic the effects of conventional drugs (e.g. cannabis, amphetamines, cocaine and LSD) but they have been structurally modified to circumvent legislative control (‘designer drugs, smart drugs’). Hence, they are advertised and sold openly through online shops (‘Internet drugs’) as legal alternatives to controlled drugs (‘legal highs’), or in terms of masked products such as ‘bath salts’, ‘plant food’ and ‘research chemicals’ [2]. The online drug shops list their best selling products and the ordered material is sent home in discreet postal items. The new

drugs thereby reach a wider customer base than the conventional illicit ones. In a survey conducted by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2012 [3], several hundred Internet resellers of recreational drugs were identified. Furthermore, during 2011 and 2012, 49 and 73 new psychoactive substances, respectively, were officially notified through the European Union early-warning system, representing the highest yearly figures reported so far.

The escalating popularity and abuse of new psychoactive substances are attracting increasing attention, due to intoxications and deaths among adolescents and young adults who are the main targets for these types of drugs [4]. For obvious reasons, the new substances have not been tested for safety, occasionally resulting in serious medical

Correspondence: Anders Helander, C1:74, Clinical Chemistry, Karolinska University Laboratory Huddinge, SE-141 86 Stockholm, Sweden. Tel: + 46 (0)8 58581293. E-mail: anders.helander@ki.se

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complications and fatalities due to toxic effects [5–7]. Furthermore, they are usually sold under different brand names with no indication of the true active ingredients or their purity [8–10]. Consequently, this increases the risk of overdose and adverse effects. The actual contents may also vary over time, such as in ‘Spice’-like products which are herbal smoking mixtures with the addition of synthetic cannabinoid receptor agonists [11,12]. The knowledge of new drugs, concerning routes of administration, dosage, and pharmacological effects, is usually shared in Internet chat forums [13,14].

New psychoactive substances are also used by drug addicts as legal alternatives and/or cheaper substitutes for the conventional drugs-of-abuse [15]. Another motive may be that the new drugs are not detected in routine drug testing which often represents an integral part of outpatient treatment programs. Although the staff may suspect their patients being intoxicated, the standard immunoassay urine drug screen turns out negative as it typically targets only the conventional set of illicit drugs (i.e. cannabis, amphetamines, opiates, cocaine and benzodiazepines).

In January 2010, the Karolinska Institutet, the Karolinska University Laboratory and the Swedish Poisons Information Centre (Stockholm, Sweden) initiated a joint nationwide project focusing on the problems with novel psychoactive drugs (the Swedish project acronym is ‘STRIDA’). A new multi-component liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method was developed, offering an attractive way to identify such substances [16–19]. The overall aim of the STRIDA project is to assess the increasing occurrence and trends of new psychoactive substance abuse and collect clinical information about prominent symptoms, toxicity and associated health risks. This initial paper focused on the particular substances identified, the population demographics of the cases, and on clinical features reported in patients with analytically confirmed exposure of different substance groups.

Materials and methods

Patients and samples

The first phase of the STRIDA project involved consecutive patients presenting at emergency departments all over Sweden. The departments had been sent an informative letter about the project, and the same information was given when the Swedish Poisons Information Centre, that serves the entire country, was contacted by clinicians with inquiries regarding cases of acute overdoses of recreational drugs. Only patients who voluntarily admitted use of new psychoactive substances or products, or in whom intoxication with such drugs was suspected by the medical staff, were included at the initial stage.

The hospital staff recorded case notes on the age, gender, clinical symptoms and treatment. Whenever available, patient self-reports on the particular drug substance and/or brand names, the dose, time of intake, and route of administration were also collected. The staff was recommended to collect blood and urine samples for toxicological analysis as soon as possible after admission. Venous blood was drawn into EDTA vacutainer tubes for preparation of plasma, and urine was collected into test tubes without additives according to routines for drugs-of-abuse testing. The samples were stored refrigerated or frozen until submitted to the Karolinska University Laboratory. Use of a special project laboratory order form allowed for free analysis of psychoactive drug contents. On arrival in the laboratory, the samples were stored refrigerated or frozen at -20°C until time of analysis. Initial analysis was typically carried out within one week.

For the scientific evaluation, the clinical and laboratory data were anonymized and only linked to the individual case by a code number. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983, and the project has been approved by the regional ethical review board.

Analysis of new psychoactive substances

The analysis of psychoactive substances in urine and plasma was carried out by a new electrospray ionization LC-MS/MS multi-component method, which was developed based on previous work [17,18]. In brief, for urinary analysis, a 5-fold dilution of the specimen with an internal standard was used, while the plasma method involved an initial protein precipitation with acetonitrile. The MS/MS detection was based on two product ions per analyte in positive selected reaction monitoring (SRM) mode. By this method, it is currently possible to monitor >100 analytes including about 80 new psychoactive substances or metabolites thereof with a limit of quantification (LOQ) at 100 ng/mL (manuscript submitted).

Additional analytical investigations

Screening for conventional drugs of abuse was performed using CEDIA, DRI or EIA reagents applied on an Olympus 640 Analyzer from Thermo Fisher Scientific. The following analytes were screened for (LOQ): Amphetamines (500 ng/mL), barbiturates (100 ng/mL), benzodiazepines (200 ng/mL), buprenorphine (5 ng/mL), cannabis (25 ng/mL), cocaine (150 ng/mL), ethanol (5 mmol/L), ethyl glucuronide (500 ng/mL), gamma-hydroxybutyrate (GHB; enzymatic method from Bühlmann Lab AG, 20 $\mu\text{g/mL}$), LSD (0.5 ng/mL), methadone (300 ng/mL), opiates (300 ng/mL), oxycodone (300 ng/mL), phencyclidine (25 ng/mL), propoxyphene

(300 ng/mL), tramadol (200 ng/mL) and creatinine (reference interval 0.30–39 mmol/L). Confirmation of positive screening findings was performed by LC-MS/MS [20–23].

Results

During the initial 12 months of the STRIDA project, 103 cases were received from patients presenting at emergency departments across the country. Altogether 37% of the cases originated from the southern part (Götaland), 43% from the central part (Svealand, including Stockholm), and 20% from the northern part (Norrland) of the country. The age range of patients was 13–54 years (mean 22.3, median 20) and 78% were 25 years or younger and 49% below 20 years. Most (81%) of the patients were males. According to information provided on the laboratory order form that followed each case, synthetic cannabinoids ('Spice'-like products) was the most commonly reported or clinically suspected type of drug (36%) followed by substituted cathinones (commonly referred to as 'bath salts'; 14%) and 'kratom' (i.e. mitragynine; 4%). In about one third (32%) of the cases, the drug was reported as 'unknown'. Self-reported routes of drug administration were oral (42%), inhalation (smoking; 41%), nasal (sniffing/snorting; 11%) and intravenous (6%); however, as expected, this largely depended on the type of drug. In 49 cases the likely origin of the drug was indicated, the far most common way being 'purchase over the Internet' (71%) followed by 'received from a friend' (10%).

In 76% of the cases, both urine and blood plasma were submitted for analysis, while only plasma (15%) or only urine (9%) was obtained in the others. Several new psychoactive substances but also conventional illicit drugs were detected (i.e. present at concentrations above the LOQ) in these samples (Table I) while 18% tested negative. In nearly half (44%) of the cases, more than one new psychoactive substance, or a mixture of new and/or conventional drugs was identified in each sample.

The detected substances have been divided into subgroups, based on their chemical structure and/or pharmacological action:

Synthetic cannabinoid receptor agonists (*'Spice' products*)

These substances are similar in action to the naturally occurring Δ -9-tetrahydrocannabinol (THC), the active ingredient in cannabis. The particular cannabinoids identified by LC-MS/MS in 22 plasma samples (21% of cases) were JWH-015, JWH-018, JWH-019/122 (not separated), JWH-081, JWH-210 and JWH-250, with JWH-081 being the single most common one (present in 59% of JWH-positive

Table I. Substances identified among 103 consecutive cases submitted for toxicological analysis within the STRIDA project on novel psychoactive drugs in Sweden.

Substances (alternative/trade names)	Positive samples ¹ , N (%)
Synthetic cannabinoids	
JWH-015	4 (3.9%)
JWH-018	3 (2.9%)
JWH-019/JWH-122 ²	2 (1.9%)
JWH-081	13 (12.6%)
JWH-210	1 (1.0%)
JWH-250	2 (1.9%)
Substituted cathinones	
Butylone (bk-MBDB)	3 (2.9%)
Flephedrone (4-fluoromethcathinone, 4-FMC)	1 (1.0%)
3-FMC (3-fluoromethcathinone)	1 (1.0%)
MDPV (3,4-methylenedioxypyrovalerone)	3 (2.9%)
Mephedrone (4-methylmethcathinone, 4-MMC)	2 (1.9%)
4-MEC (4-methylethcathinone)	1 (1.0%)
Methcathinone (ephedrone, α -methylamino-propionophenone)	1 (1.0%)
Methylone (bk-MDMA)	4 (3.9%)
Substituted tryptamines	
4-HO-MET (4-hydroxy-N-methyl- N-ethyltryptamine)	8 (7.8%)
Plant- or fungi-derived substances	
Mitragynine (kratom)	4 (3.9%)
Psilocin (4-hydroxy-N,N-dimethyl- tryptamine, 4-OH-DMT)	1 (1.0%)
Pharmaceutical agents	
Benzodiazepines	21 (20.4%)
Desoxypipradrol (2-DPMP, 2-diphenylmethylpiperidine)	3 (2.9%)
Dextromethorphan (DXM)	1 (1.0%)
Ethylmorphine	1 (1.0%)
Phenazepam	3 (2.9%)
Pregabalin (Lyrica®)	6 (5.8%)
Tramadol/O-desmethyltramadol ³	9 (8.7%)
Remaining and conventional drugs	
4-Fluoroamphetamine (4-FA, 4-FMP)	2 (1.9%)
4-Methylamphetamine (4-MA)	3 (2.9%)
Methoxetamine (MXE, Mket)	1 (1.0%)
GHB (gamma-hydroxybutyric acid)	1 (1.0%)
Buprenorphine	1 (1.0%)
Methadone	2 (1.9%)
Amphetamine/Methamphetamine	8 (7.8%)
Cannabis	18 (17.5%)
Cocaine	1 (1.0%)
Opiates	4 (3.9%)
Ethanol (ethanol and/or ethyl glucuronide; EtG)	27 (26.2%)

¹Concentration $\geq$ LOQ. Several samples contained more than one new psychoactive substance, or a mixture of new and conventional drugs, or conventional drugs only, while 19 (18%) tested negative.

²Not separated in the LC-MS/MS analysis. ³Two samples tested positive for tramadol only, four were positive for both tramadol and O-desmethyltramadol, while three were positive for O-desmethyltramadol only.

samples) (Table I). The synthetic cannabinoids (i.e. parent compounds) were detected in samples of plasma but not in the corresponding urines, because JWH metabolites were initially not tested for. The age range of patients having used this type of drugs was 13–54 years (mean 20.4, median 18.5) and 78%

Table II. Main psychoactive substance groups in the STRIDA project, commonly reported symptoms among the clinical cases, and published data supporting the observed symptoms.

Psychoactive substance group (<i>N</i> cases)	Common symptoms reported among the clinical cases* (%)	References supporting the symptoms observed
Cannabinoid receptor agonists (22 cases)	Tachycardia (77%) Mydriasis (73%) Drowsiness/somnolence (36%) Myoclonus/tremor (27%) Agitation/restlessness (23%) Hypertension (23%) Nausea/vomiting (23%)	[12,33,34]
Substituted cathinones (11 cases)	Tachycardia (64%) Agitation/restlessness (64%) Mydriasis (55%) Hypertension (45%) Hallucinations (27%) Myoclonus/tremor (27%)	[2,7,35]
Substituted tryptamines (8 cases)	Agitation/restlessness (75%) Mydriasis (75%) Tachycardia (63%) Nausea/vomiting (50%) Hallucinations (38%)	[5,14]

*Hospital case records were available in 96 of 103 cases (93%).

were males. Inhalation (smoking) was the only reported route of drug administration.

According to the case records, tachycardia, mydriasis, drowsiness/somnolence, myoclonus/tremor, agitation/restlessness, mild hypertension and nausea/vomiting were the most frequent clinical symptoms reported in patients taking synthetic cannabinoids (Table II).

Substituted cathinones ('bath salts')

These substances are derivatives of cathinone, the main active substance in leaves of *Catha edulis* (abused under the name of 'khat'). Cathinones are stimulants with effects similar to that of amphetamines and ecstasy. The specific drugs detected in 11 urine samples (11% of cases) were butylone, flephedrone, 3-FMC (3-fluoromethcathinone), MDPV (3,4-methylenedioxypyrovalerone), mephedrone, 4-MEC (4-methylethcathinone), methcathinone and methylone (Table I). Methylone was the single most common substance and was detected in 36% of the cathinone-positive samples. The age range of patients having used this type of drugs was 19–32 years (mean 25.2, median 25.0) and 91% were males. Oral intake was the only reported route of drug administration.

Prominent clinical symptoms reported for patients taking substituted cathinones were tachycardia, agitation/restlessness, mydriasis, hypertension, myoclonus/tremor and hallucinations (Table II).

Substituted tryptamines

These substances are derivatives of the naturally occurring tryptamines. The only tryptamine detected among the initial 103 cases in the STRIDA project

was 4-HO-MET (4-hydroxy-N-methyl-N-ethyl-tryptamine) (Table I). The age range of the eight patients having used this substance was 17–32 years (mean 23.1, median 22.0) and all were males. Oral drug intake was reported in five cases (62.5%) and nasal intake in the remaining (37.5%) ones.

Characteristic clinical effects reported after intake of 4-HO-MET were mydriasis, agitation/restlessness, tachycardia, nausea/vomiting and hallucinations (Table II). Interestingly, half of the cases of 4-HO-MET intoxication originated from the same small town located in southeastern Sweden.

Pharmaceutical agents

Besides common benzodiazepines (e.g. diazepam, oxazepam and temazepam) that were found in 20% of the samples, and possibly might have been administered at the emergency departments [15], the pharmaceutical agents detected were tramadol/O-desmethyltramadol, pregabalin, phenazepam, desoxypipradrol, dextromethorphan and ethylmorphine (Table I). The age range of the 23 patients exposed to any of these latter drugs was 15–54 years (mean 22.3, median 21.0) and 74% were males. Except for phenazepam (a long-acting benzodiazepine) and dextromethorphan (cough suppressant), the pharmaceutical agents were typically (~85% of cases) found in combination with one or more new and/or conventional psychoactive substance.

All three single-agent intoxications with phenazepam (nasal intake in two men and one woman, aged 17–24 years) originated from the same small town located in the central part of Sweden. The reported clinical effects included drowsiness, slurred speech, ataxia and somnolence.

Plant- or fungi-based substances

The only plant/fungi-based substances detected among the 103 initial STRIDA cases were mitragynin and psilocin (Table I). Mitragynin originates from *Mitragyna speciosa*, a tree that grows in South-East Asia, and it is usually sold as 'kratom'. The compound recently has attracted attention in connection with deaths linked to a particular kratom product named 'Krypton' that also contains O-desmethyl-tramadol [6,24]. In one case, mitragynine and O-desmethyltramadol but no tramadol were detected, thus indicating use of Krypton. The four patients (three men and one woman) who tested positive for mitragynine were aged 20–43 years (mean 27.5, median 23.5).

Psilocybin occurs in 'magic mushrooms' primarily of the genus *Psilocybe* (e.g. liberty cap). The body rapidly converts psilocybin into psilocin which exercises the main psychoactive (hallucinogenic) effect. The single patient who tested positive for psilocin was a 25-year-old male reporting oral intake.

Remaining and conventional substances

This final substance group included conventional drugs-of-abuse but also occasional cases of new psychoactive substances (4-fluoroamphetamine, 4-methylamphetamine and methoxetamine) (Table I).

Discussion

The initial results of the STRIDA project have documented use of a broad variety of new psychoactive substances among mainly male adolescents and young adults in Sweden. The clinical cases originated from all over the country, which was not unexpected given these drugs are easily accessible online from suppliers on the Internet. However, local outbreaks of abuse of particular substances (e.g. 4-HO-MET and phenazepam) were also discovered.

Laboratory detection of new psychoactive substances became possible through the development of an LC-MS/MS multi-component method (manuscript submitted), that currently allows for the identification of about 80 new compounds or metabolites thereof. With a few exceptions, detection of the new substances is not possible with the standard central laboratory or on-site immunochemical-based assays intended for routine urine drug screening. The substances detected by LC-MS/MS comprised synthetic cannabinoids ('Spice'; JWH analogues), substituted cathinones ('bath salts'; e.g. MDPV, butylone, methylone and mephedrone) and tryptamines (4-HO-MET), plant-based substances (mitragynine and psilocin) and pharmaceutical agents, as well as conventional recreational drugs.

Close to one fifth of the samples tested negative for drugs. Among the patients admitting drug use,

this was likely due to a too long time elapsing between intake and sampling (data not shown), although it should be noted that the detection windows for many new psychoactive substances are not yet established. On the other hand, negative test results in patients suspected to be intoxicated might also have been due to an incorrect assessment of the medical staff. In addition, an important analytical observation that will influence the likelihood of a positive test result was that synthetic cannabinoids (i.e. parent JWH compounds) and phenazepam were detected only in samples of blood plasma but not in the corresponding urine samples. For urinary analysis of synthetic cannabinoids, measurement of drug metabolites is required [25,26].

The clinical information gathered in the STRIDA project indicated a number of adverse effects associated with exposure to new psychoactive substances (Table II), some of which have been confirmed in recent reports [2,15,27–29]. An apparent difference, however, was the lack of hallucinations among the present cases. There are still limited data on clinical symptoms and toxicity for most of the new substances, given they have not been tested clinically and in general have only been available for a short time on the recreational drug market [5]. Furthermore, the information provided by online shops and through Internet chat forums speaks rather of their alleged psychoactive (i.e. 'positive') effects.

The increasing sale of 'legal' recreational drugs-of-abuse through the Internet has brought a new and alarming drug trend that is attracting much attention. Current legislations are mostly not effective or rapid enough to take action against the availability of new potentially harmful psychoactive substances, before they have been evaluated from a toxicological standpoint and formally classified. The Swedish legal system, for example, does not apply generic classification of drugs but each substance has to be regulated individually which is currently possible by two controlling laws. From the time a new potentially hazardous substance abuse is recognized, it usually takes at least six months to settle it as 'dangerous to health' and even longer as a 'narcotic' drug. In recent years, a number of novel substances that were initially classified as dangerous to health were later reclassified as a narcotic substance. Classification as a narcotic drug usually implies the open sale from online shops based within the country ceases. Once in the process of becoming classified, such products are typically put on sale and rapidly replaced by other yet non-controlled ones. However, substances classified as dangerous to health have often continued to be sold openly (e.g. 2C-E, 5-MeO-DMT, JWH-122 and TFMPP), probably because the penalty is much lesser compared to narcotic drug offenses. Banned drugs also continue to be available over the Internet from suppliers based abroad [30].

In conclusion, through STRIDA, a nationwide project has become available to assess the occurrence and trends of abuse of novel psychoactive drugs, and collect information about their prominent clinical symptoms, toxicity and associated harms. The new LC-MS/MS multi-component method makes it possible to identify a large number of new compounds in samples of urine and/or blood, which was previously not possible. Given the initial strategy to focus mainly on intoxicated patients presenting at emergency departments [31], the project has so far probably identified the most dangerous substances and the most severe clinical cases. Although the exact frequency of new psychoactive substance use is unknown, the project is likely to identify the substances that are currently circulating in the country. The clinical and analytical information gathered in this way represent a valuable complement to other sources, such as forensic data on deaths and analysis of material seized by the customs and police, in the clinical assessment of cases of poisoning and as a basis for legal classification of new psychoactive substances. In this context, the STRIDA project has a continuous exchange of experiences, and of chemical reference standards, with several partners within the country (the National Institute of Public Health, the Medical Products Agency, the National Board of Forensic Medicine, the Swedish Customs' Laboratory and the National Laboratory of Forensic Science). Finally, it should be noted that the LC-MS/MS multi-component method for analysis of new psychoactive substances has also been put into routine use, for testing of a large number of samples originating mainly from addiction treatment and substance abuse centers.

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